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TITLE OF THE INVENTION (280 characters max)

A BIORESPONSIVE POLYMER SYSTEM FOR THE DELIVERY OF MICROBICIDES

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Respectfully submitted,

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TITLE:

A BIORESPONSIVE POLYMER SYSTEM FOR THE DELIVERY OF MICROBICIDES

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A BIORESPONSIVE POLYMER SYSTEM FOR THE DELIVERY OF MICROBICIDES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention provides compositions and methods for a bioresponsive polymer system capable of a change in morphology and/or viscosity upon contact with an ejaculate. Such system may be used to delivery a microbicide for the prevention of sexually transmitted diseases, promotion of fertility, prevention of fertility and/or hormone replacement therapy.

Description of the Related Art

Approximately 40 million people worldwide are living with HIV/AIDS, and new diagnoses are occurring at a rate of approximately 12% per year. There is currently no cure for HIV/AIDS and research on pharmaceuticals and vaccinations to treat and/or prevent the disease are complicated by ongoing mutations of the viral DNA. Therefore, even the vaccinations currently being developed may only protect the population from a small fraction of the known HIV types due to the rapid mutation rate of the virus.

Microbicides are topical chemical agents that can block sexually transmitted diseases, including HIV. Referred to as "chemical condoms", they are formulated into gels, creams, foams, impregnated sponges, suppositories, or films for insertion into the vagina or rectum prior to intercourse. However use of currently available microbicides is not without risk as they have been shown to make the user more vulnerable to infection by damaging the protective epithelial layer thereby leaving the infection-prone lower layers exposed. Additionally, current microbicide formulations do not promote retention in the vagina or rectum.

The development of a microbicide capable of maintaining the epithelial layer of the oral, vaginal or rectal cavity, while also maintaining a physical structure that

promotes retention once applied, would provide an improved method of preventing sexually transmitted diseases.

Summary of the Invention

In accordance with the purpose(s) of this invention, as embodied and broadly described herein, this invention, in one aspect, relates to a polymer system that demonstrates a change in viscosity or modulus upon exposure to an ejaculate. The polymer system may further provide microbicides which are released upon exposure of the polymer system to an ejaculate (See Figure 1). In particular embodiments, the components of an ejaculate that may induce a physical or chemical change in the polymer system include ions, sugars, surfactants, proteolytic and other enzymes and the like (See Table 1). These components and in particular enzymes (see Table 2) can be used to induce a reduction in viscosity or modulus in a polymer system. In some cases it may be advantageous to have the gel go from a cream like material to a soluble polymer system or from a hydrogel like material to a soluble polymer system. In a particular embodiment, the microbicide is conjugated to the polymer system. The polymer system of the present invention can be utilized as a method of preventing sexually transmitted diseases, as a method of preventing or promoting fertility and/or as a method of hormone replacement in an individual.

Detailed Description

The present invention may be understood more readily by reference to the following detailed description of particular embodiments of the invention and Examples included therein.

Particular advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and

the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

Before the present invention and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific reagents or synthetic procedures, as such may, of course, vary, unless it is otherwise indicated. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Figures

The following tables and drawings form part of the present specification and are included to further demonstrate certain embodiments. These embodiments may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

Table 1 illustrates exemplary components of a human ejaculate according to one embodiment of the present invention.

Table 2 illustrates exemplary enzymes present in a human ejaculate in accordance with an embodiment of the present invention.

Table 3 illustrates exemplary monomers which may be utilized in the polymer systems of the present invention.

Figure 1 illustrates the viscosity change a particular polymer system undergoes in the presence of an ejaculate according to the present invention. At time point (A), the polymer system is in an orifice of an individual, such as the vagina or rectal cavity. At time point (B), the polymer system comes in contact with an ejaculate. Upon contact with an ejaculate, the polymer system is disrupted and the viscosity is reduced (C).

Figure 2 illustrates a linear chain degradable polymer system according to one embodiment of the present invention wherein (A) is a degradable sequence, (B) is a polymer filament, (C) is a component in an ejaculate which cleaves the degradable sequence, (D) is a remaining moiety resulting from cleavage of the polymer backbone and (E) is also a remaining moiety resulting from cleavage of the polymer backbone.

Figure 3 illustrates a linear chain degradable polymer system made with variable blocks of polymer filaments wherein (A) is a water soluble polymer filament, (B) is a degradable sequence, (C) is a water insoluble polymer filament, (D) is a water soluble polymer filament, (G) is a component in an ejaculate which cleaves the degradable sequence, (F) is a remaining moiety resulting from cleavage of the polymer backbone and (E) is another remaining moiety resulting from cleavage of the polymer backbone according to one embodiment of the present invention.

Figure 4 illustrates degradation of covalent, hydrogen, or ionic bonds which form crosslinks between polymer chains according to an embodiment of the present invention. In this particular embodiment, (A) is polymer component 1, (B) is a degradable sequence, (C) is cross-linking moiety 1, (D) is cross-linking moiety 2, (E) is polymer component 2, (F) is a component in an ejaculate that interacts with (B) and cleaves it into two parts (G) and (H).

Figure 5 illustrates an interpenetrating polymer network according to one embodiment of the present invention. In this illustration, (A) is a water soluble polymer filament 1 containing cross-linking moieties (D) which allow polymer filament (A) to independently form micelles (C). (B) is a water soluble polymer filament 2, which also contains cross-linked moieties containing degradable sequences. (B) forms micelles (C), which may be formed by cross-linking moieties (D) which are the same as or different from the cross-linking moieties of polymer filament (A). A mixture of (A) and (B) forms an interpenetrating network gel. The viscosity of the gel is reduced when the cross-linking moieties (D) in the micelles (C) are degraded.

Figure 6 illustrates the synthesis of a polymer system of Figure 5.

Figure 7 illustrates the rheological properties of a two component polymer system before and after mixing the components according to an embodiment of the present invention.

Figure 8 illustrates a change in viscosity of a polymer system after addition of ejaculate stimulant in accordance with an embodiment of the present invention.

Figure 9 illustrates a self-associated degradable polymer system in accordance with an embodiment of the present invention. In this illustration, polymer 1 contains degradable sequences (B) and micelle forming hydrophobic chains (C). In the presence of an ejaculate containing component (D), degradable sequences (B) are cleaved into fragments (F) and (G). Polymer (A), comprising fragment (F), and hydrophobic micelle chain (E), comprising fragment (G), are thereby severed.

Figure 10 illustrates the displacement of an interaction between two chains by a component in an ejaculate according to an embodiment of the present invention. This figure illustrates polymer components (A) and (E) interacting via moieties (B) and (C) to form a temporary crosslink. In the presence of an ejaculate including component (D), (B) is displaced by (D) and the crosslinks are broken between polymer (A) and (E).

Figure 11 illustrates the degradation of a crosslinker by a component in an ejaculate according to an embodiment of the present invention. The figure illustrates polymer component 1 (A) interacting through crosslinks to polymer component 2 (E). In the presence of an ejaculate which contains component (F) the crosslinks are disrupted between polymer 1 and 2.

Figure 12 illustrates another mechanism of degrading a crosslinker by a component in an ejaculate according to the present invention. In this instance, polymer 1(A) and polymer 2 (F) are crosslinked by ionic interactions (C) between polymer-bound

moieties (D) and ionic components (S). In the presence of an ejaculate, a component of which is an ionic complexing agent (E), the crosslink is broken through competition by (E) for ionic component S.

Figure 13 illustrates degradation of ionically crosslinked polymers according to an embodiment of the present invention. In this instance, polymer 1 (A) interacts with polymer 2 (F) via ionic interactions between opposing groups (B and D) on each polymer. The addition of an ejaculate which includes component (E) disrupts these ionic interactions and breaks the ionic bonds.

Definitions

For the purposes of the present invention, the following terms shall have the following meanings:

For purposes of the present invention, the term, "microbicide" will refer to any agent that prevents, treats, inactivates, degrades or in any other way affects a causal agent of a sexually transmitted disease. Examples of such agents include antiviral drugs, traditional microbicides that destroy microbes, such as viruses and bacteria, and the like. Additionally, the term will further include any agent that prevents or promotes fertility. Such agents may be useful in in-vitro fertilization procedures, as a family planning methodology and/or as a way to supplement a particular hormone or combination of hormones in an individual.

For the purposes of the present invention, the term "prevent" shall be understood to mean "to reduce or completely eliminate the likelihood of something occurring". Therefore, preventing the spread of sexually transmitted diseases is synonymous with decreasing the probability of contracting a sexually transmitted disease.

Moreover, for the purposes of the present invention, the term "a" or "an" entity refers to one or more of that entity, for example, "a protein" or "an enzyme" refers to one or more of those elements or at least one element. As such, the terms "a" and "an", "one

or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. Furthermore, "selected from the group consisting of" refers to one or more of the elements in the list that follows, including mixtures (i.e. combinations) of two or more of the elements.

For the purposes of the present invention, ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about", it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

Reference will now be made in detail to particular embodiments of the invention.

The present invention embodies compositions and methods related to a novel method of preventing the transmission of a sexually transmitted disease in an individual. The present invention also provides a method of promoting or preventing fertility in an individual. The present invention further provides a method of supplementing a hormone or combination of hormones in an individual.

Polymer Systems

To design effective bioresponsive polymer systems, an understanding of the target and its interaction with the physiology of the vaginal, rectal or oral cavity is necessary.

In the case of a polymer system further providing a microbicide directed towards inactivation or degradation of HIV, an understanding of the human female reproductive tract is critical. Potential sources of HIV are free virus, infected lymphatic cells in semen, and HIV in other fluids which may be present due to trauma. For free virus, the route of

infection is well understood. The HIV surface envelope gp120 protein binds the cell surface receptor CD4; this is then followed by interactions with co-receptors and viral conformational changes which result in fusion of the HIV lipid bilayer with the target cell surface. The cells of the vaginal squamous epithelium are not thought to be susceptible to HIV infection as they do not express the necessary receptors, but the lymphoid cells in the epithelium and the lamina propria are potential sources of early infection. Once infected, dendritic cells carrying the virus on their surface or internally can migrate to lymphoid tissue and spread the virus throughout the body. The question of how the HIV virus can infect the cells protected in the lamina propria is still an area of contention, but the dominant hypothesis suggests that infection can only occur if the epithelium is damaged, thereby permitting access by the HIV particles or infected cells to the lower layer.

Currently available microbicides for the prevention of fertility and/or sexually transmitted diseases, such as nonoxynol-9 (N-9), are not ideal delivery mechanisms for the female vagina. Under ideal mixing conditions nonoxynol-9 (N-9) is a very potent spermicide *in vitro*, yet *in vivo* N-9 formulations are not effective contraceptives or microbicides. This lack of effectiveness is likely due to poor mixing properties and ineffective biodistribution/deployment in the reproductive tract. It is clear from the poor performance of N-9 as a contraceptive and as a potential microbicide that the classical formulations approach alone will not result in a highly effective microbicide.

To design the ultimate microbicide, a number of functional attributes must be considered and addressed. Additionally, a thorough understanding of the needs and preferences of women is critical to the design. Such considerations include ease of use, cosmetic acceptability, and enhancement of sexual pleasure. In addition, the material must exhibit no cytotoxicity with prolonged use, must promote the inactivation of HIV (both free and cell associated) and other causal agents of sexually transmitted diseases, should protect and reinforce of the normal physiology of the vagina, and must distribute itself to form a protective barrier across the vagina, rugae, and cervix to prevent the interaction of a sexually transmitted disease causal agent or other pathogens with tissue.

Ideally, the vehicle will minimize the systemic bioavailability of the agent to ameliorate side effects and toxicity during repeated use. The active agent should have maximum topical bioavailability to inactivate free and cell associated virus. The material also must be retained in the vagina after application for several hours. Finally, there should be a simple and effective means for its removal from the body along with the ejaculate, which carries the infecting agent. Further constraints on polymer systems containing microbicide include but are not limited to long term stability, low cost production, and chemical compatibility with latex and other barrier devices.

The polymer systems containing microbicides of the present invention exhibit specific rheological characteristics such as the existence of yield stresses and sheer thinning. The presence of yield stresses is thought to aid in retention before intercourse. Sheer thinning will also promote the ability of the material to be spread before and during intercourse. Moreover, there is strong rationale to engineer the microbicide's rheological, adhesive and diffusive properties to respond to signals (e.g. seminal proteases) present in the vagina to enable and enhance different phases of microbicide deployment.

The polymer systems containing microbicides of the present invention will undergo triggered rheological changes when applied to the lower reproductive tract, and also when initially contacted by an ejaculate. This way the material will be a liquid during application, thereby promoting penetration, ease of use and coating. It can then gel while in the vaginal, rectal or oral cavity promoting coating, retention and decreased bioavailability of the encapsulated active agent. Finally, when in contact with an ejaculate the vehicle will undergo liquefaction and release the microbicide and be removed by gravity or other forces from the body. During this process, a molecular layer of polymer will be left behind to provide a continued level of protection to the tissue.

The polymer systems of the present invention are bioresponsive to the oral, rectal or vaginal cavity in which they are placed and optimized for the functional requirements of microbicides. In a particular embodiment, the polymer systems of the present invention (1) are known to be biocompatible, (2) are known to be able to encapsulate

both hydrophilic and hydrophobic drugs, (3) are engineered to be applied as a low viscosity fluid in two components, (4) will undergo mixing induced gelation in the body cavity, (5) will undergo sheer thinning and exhibit yield/residual stresses, (6) will bioadhere to mucosal tissue and (7) will undergo liquefaction when in contact with seminal components and be readily removed from the body cavity.

Any polymer known in the art may be used in the present invention. In particular embodiments, the polymer is a preformed polymer which is then suitably modified. Modifications, including polymerization with a wide variety of described functionalities, are well known in the art. In another particular embodiment, the polymer system is described as being composed of two distinct polymers which form the polymer system. In this case the two distinct polymers may be of the same chemical class of polymers or different classes. In another particular embodiment, the polymers are water soluble resulting in cross-linked polymers, such as in a hydrogel or high viscosity cream.

The polymers of use in the present invention, include but are not limited to, the class of water soluble synthetic polymers: such as ethylene glycol, poly(ethylene) glycol, poly(ethylene oxide), poly(vinylpyrolidone), poly(ethylene oxide)-co-poly(propylene oxide), and poly(ethyloxazoline), poly(urethanes), poly(vinyl alcohol), carboxymethycellulose, cellulose acetate, modified celluloses, dextran, nylons, carboxymethylcellulose and carbopols and their copolymers graft comb polymers and derivatives. Additionally, the class of water soluble polymers include the water soluble natural polymers, including but not limited to: poly(saccharides), proteins, poly(aminoacids) alginates, chondroitin sulphate, chitosan, heparin, hyaluronic acid, deoxyribonucleic acid, poly(aminoacids) and other sugar containing polymers and their copolymers and derivatives.

In another embodiment of the present invention, polymers include acrylate based polymers which are formed from acrylate based monomers which include, but are not limited to, 2-hydroxypropylmethacrylamide, 2-hydroxyethyacrylate, acrylic acid, methacrylic acid and other similar monomers. Additionally, co-polymers, block

copolymers and their derivatives may be used in the present invention and may be formed by free radical, anionic or cationic polymerization, ring opening metathesis polymerization (ROMP), and other known methods.

In another embodiment of the present invention, hydrophobic degradable polymers and their oligomers may be used as components in the polymer system as long as the required water solubility is not compromised. Polymers of this type include, but are not limited to, the poly(esters), poly(ethers), poly(caprolactone), poly(valerolactone), poly(α-hydroxyesters) and their copolymers and derivatives.

Degradable Sequences

Degradable sequences may be used in the present invention. For example, particular types of sequences are those that are susceptible to chemical, physical or enzymatic degradation. Chemical degradation is largely isolated to functional groups which are likely stable in the natural pH of the vagina of approximately 4-5 while becoming unstable in the presence of a higher pH, such as 7.5 which is found in an ejaculate. Chemical functionalities that fit this description include, but are not limited to, esters, such as oligomers of the alpha-hydroxyesters, amides, imides, and the like. Degradable sequences may be chemically cleaved by acids, bases, alcohols, and chelating agents, for example. In a particular embodiment, the degradable sequences are oligomers of alpha-hydroxyesters that degrade rapidly via based-promoted hydrolysis, where the base is a part of an ejaculate. Oligomers of N=2 to 6 of glycolic acid esters are included in this embodiment. In embodiments for use in the rectum, enzymatic degradation sequences may be utilized.

Degradable sequences may alternatively be cleaved by physical means, such as changes in temperature and pressure, for example.

Degradation may also occur via proteolytic enzymes in an ejaculate. One such enzyme, Prostate Specific Antigen, is known to cleave peptides with chymotrypsin- and trypsin- like substrate specificity. In a particular embodiment of the present

invention, the cleavable peptide sequences include Arg-Pro-Tyr and Lys-Val-Tyr sequences. Other sequences such as those present in PSA's natural substrate semenogellin and semenogellin related proteins may also be utilized in the methods of the present invention. In another particular embodiment, the peptide sequence SSIYSQTEEQ and shorter chain homologs may be utilized. The shorter chain homologs may further include serine and tyrosine. In another particular embodiment, peptides containing a positively charged amino acid in the first position, a neutral amino acid in the second position and tyrosine in third position are utilized. They may further include homologs containing additional amino acids on both the C and N terminus of this sequence.

Degradation may also be triggered by low levels of proteolyic enzymes found in an ejaculate, such as peptidases and hyaluronidases, which may further act to trigger changes in the viscosity of the gel. In a particular embodiment where hyaluronidases are utilized to trigger a degradation sequence, a hyaluronic acid based polymer or a polymer containing sub-units of hyaluronic acid would be utilized. Additional examples of enzymes found in an ejaculate and their substrates are given in Table 2.

In particular modes of the invention it may be desirable to take a suitably protected or unprotected degradable sequence and produce a reactive conjugate to attach it within or to one or more of the polymers of the polymer system in order to construct a suitable architecture for the polymer system. This material is referred to as a degradable sequence conjugate (DSC). In some cases the terminating functional groups for the DSC will be the same or different depending on the polymer architecture of the polymer system and the requirements of the mode of the invention.

Other enzymes found in an ejaculate that have the ability to cause degradation include but are not limited to alpha and beta glucosidase, Lysophospholipases, lysozyme, mannosidases, pepsinogen I, pepsinogen II, pepsinogen III, phospholipase and the like.

Creation of Polymer System

Polymer systems containing degradable sequences of the present invention may be made by any method known in the art.

In one embodiment, the polymer system will gel via a cooperative process, in which each polymer component alone will not gel but mixing of the polymer components results in formation of a gel.A conservative Michaelis-Menten kinetic model based on PSA kinetic constants (V_{max} $8x10^{-5}$ mmol/min/mg), the concentration of PSA in seminal plasma (6 mg/ejaculate), a Km of 1 mM and the estimated loading of peptide on the polymer (10 mol% gives ~0.1 mmol/3 mL of formulation) indicates the gel will be significantly degraded (~50%) in two hours. In a particular embodiment, sugar specific mucoadhesive moieties can be included in the polymer backbone which will promote coating to the epithelium of the oral, vaginal or rectal mucosa and also may bind to HIV glycoproteins. The micelles may aid in increasing the solubility of lipophilic drugs and should provide the same functionality with nevaripine which has a low aqueous solubility (~0.1 mg/mL).

In another embodiment a polymer system may be created by placing a degradable sequence between segments of the polymer filament by stepwise construction or by linking together prepolymer filaments into a larger architecture (Figure 2). Additionally, water soluble linear prepolymer filaments can be copolymerized into a higher molecular weight linear structure with degradable sequences between the prepolymer segments. Alternatively, the α-end functional group of the polymer filament which contains the degradable sequence can be polymerized with the ω functional group of the same type of polymer filament generating a high molecular weight structure. In a particular embodiment, the linear prepolymer filament is poly(ethylene glycol). Other water soluble synthetic polymer filaments and water soluble natural polymer filaments, such as suitably functionalized telechelic polymers, could also be used and the components (A) and (B) in Figure 2 can be assembled using suitable linking chemistry known to those skilled in the art.

In a particular embodiment, the degradable sequence (A) illustrated in Figure 2 is a peptide or sugar that is cleavable by proteases or other enzymes in an ejaculate.

In another particular embodiment, a telechelic α-hydroxy and ω-carboxylic acid pre-polymer containing the degradable sequence on one end can be constructed which is then polymerized with identical pre-polymer fragments or a similar polymer using standard condensation conditions in order to construct a degradable high molecular weight architecture.

In another embodiment, the degradable sequence (A) in Figure 2 may have a homo-bifunctional reactive group at both ends of the degradable sequence which will react with a suitably functionalized α,ω-telechelic polymer much like the manner of a urethane. In this embodiment a diisocyanate degradable sequence conjugate where the degradable sequence sits between the isocyanate reactive groups can be condensed with a α,ω-diol using methods known to those skilled in the art. Many other reactive group chemistries, such as this one, may be used in the present invention and are known to those skilled in this art.

In another embodiment soluble proteins are assembled with degradable sequences interspersed within a sequence of synthetic aminoacids similar to semenogelins.

Polymers (B) of use in Figure 2 with the present invention include, but are not limited to, poly(aminoacids), ethylene glycol oligomer, poly(ethylene) glycol, poly(ethylene oxide), poly(vinylpyrolidone), poly(ethylene oxide)-co-poly(propylene oxide), poly(ethyloxazoline), dextran, poly(vinylpyrolidone), nylons and urethanes, and their copolymers and derivatives with a plurality of degradable sequences interspersed along the chain.

In an additional embodiment, one may use a hyaluronic acid gel or a hyaluronic acid conjugated with hydrophobic groups or water soluble polymer filaments in the form of a graft comb polymer, where the degradable sequence (A) of Figure 2 is naturally

incorporated in the polymer backbone. In this embodiment the polymer would be degraded by hyaluronidase in the ejaculate into a lower molecular weight polymer with a lower viscosity.

Figure 3 illustrates a linear chain degradable polymer system made with variable blocks of polymer filaments. In this embodiment, degradable sequences (**B**) are attached between blocks of polymer filaments (A, C, D) in **ABCBD** type block co-polymer fashion. Here a degradable sequence is inserted between the (A) and (C) polymer filaments and the (C) and (D) polymer filaments in Figure 3 forming a triblock polymer with two degradable sequences (B). (A) and (D) can be comprised of polymer filaments from the class of water soluble polymers, and the (C) block can be comprised of a water insoluble polymer filament. Alternatively, all polymer filaments in Figure 3 can be composed of polymer filaments from the class of water soluble polymers. Additionally, (A) and (D) can comprised of polymer filaments from the class of water insoluble polymers and the (D) block can be comprised of a water soluble polymer filament.

It will be understood by those skilled in the art that the embodiment of Figure 3 may be synthesized with varying numbers of polymer filaments and/or degradable sequences. In a particular embodiment, the degradable sequence (B) is a peptide or sugar that is cleavable by proteases or other enzymes in an ejaculate.

In a particular embodiment, mono-functional polymer filaments, for example (A) and (D) of Figure 3, would be end-capped with suitably functionalized degradable sequences (B). Two of these polymeric molecules can then be reacted with an α,ω-telechelic polymer (C) to form the ABCBD architecture. Alternatively, the (C) polymer filament can be capped at both ends and this could be reacted with suitably functionalized (A) and (D) polymer filaments to form the ABCBD architecture.

In another particular embodiment, the (A) and (D) blocks of Figure 3 are mono reactive poly(ethylene oxide) and the (C) block is a α,ω-diol poly-propylene oxide or poly(ethylene oxide). To synthesize these compounds, one can conjugate (A) and (D) to a

degradable sequence. Molecules of this DSC bound to (A) and (D) can then be reacted with a suitably α,ω-functionalized poly(propylene oxide) block to form the polymer system.

In another particular embodiment, an α,ω-telechelic diol poly(propylene oxide) block water insoluble polymer filament is reacted with a carboxy terminated DSC which is attached to polymer filament (A) of Figure 3, where (A) is poly(ethylene oxide).

In another particular embodiment, an α,ω-telechelic diamine of a water insoluble polymer filament is used for the polymer filament (C) of Figure 3, and is reacted with a carboxylic acid terminus of a peptide DSC to form a bis-functionalized polymeric DSC of filament (C), which is then reacted with a suitably functionalized polymer filament (A) or (D) to form the polymer system.

In another particular embodiment, a α,ω-telechelic polymer filament (C) diacid block is reacted with the N terminus of a peptide DSC to form a bis-functionalized polymeric DSC, which is then reacted with a suitably functionalized polymer filament (A) and/or (D).

In another embodiment, an α,ω-telechelic polymer filament diacid (C) block could be reacted with a hydroxyl functionalized DSC containing the (A) and/or (D) block.

In another embodiment, the polymers that are suitable for the Figure 3 filaments (A) and (D) are end functionalized water soluble polymers including, thiol terminated 2-hydroxypropyl methacrylamide, thiol terminated hydroxyethyl methacrylate and other end functionalized acrylate polymers. Included in the hydrophobic (C) block are polymers such as poly(esters), poly(saccharides), poly(propylene oxide), poly(carbonates) and other non-water soluble polymers.

Figure 4 illustrates the degradation of covalent, hydrogen, or ionic bonding crosslinks between polymer chains. In this embodiment, a polymer filament (A) is constructed in such a way that it is functionalized with at least one degradable sequence conjugate (DSC) terminated with at least one bonding moiety (C) that can interact through covalent, hydrogen, and/or ionic bonding with a complimentary bonding moiety (D) on another polymer filament (E) of the polymer system. When exposed to the appropriate component in an ejaculate the degradable sequence(s) (B) will be cleaved and the viscosity or modulus of the polymer system will then be reduced.

In Figure 4, (A) and (E) may be the same or different polymer filaments. In a particular embodiment, polymer filaments (A) and (E) are water soluble natural polymers or water soluble synthetic polymer filaments. In another particular embodiment, the degradable sequence (B) is a peptide or sugar capable of cleavage by proteases or enzymes in an ejaculate. The (C to D) connection shown in Figure 4, can be made through electrostatic interactions based on the Cyanuric Acid·Melamine pair or through other suitable donor -acceptor interactions.

In another particular embodiment, the (C to D) interaction of Figure 4 is covalent in nature and involves the use of carbon-carbon, carbon-oxygen, carbon-sulfur, sulfur-sulfur or carbon-nitrogen bonds to link the filaments (A) and (E) together via suitable linking chemistry. In a particular embodiment, the degradable sequence (B) is terminated in a thiol and the complimentary bonding moiety (D) contains a Michael acceptor such as an α,β-unsaturated ester or ketone, a vinylic sulfone, or another suitable Michael acceptor. When the thiol is mixed with the Michael acceptor, crosslinking will occur and a higher molecular weight structure will be produced.

In another particular embodiment, polymer filament (A) of Figure 4 is a water soluble polymer and degradable sequence (B) is a sequence made up of a peptide susceptible to PSA which is attached to (A) through suitable reactive groups including thiol, alcohol, amine, carboxylic acid carbonate, carbamate, hydrazone, hydrazine,

aldehyde, cyclic ether, acid halide, acyl azide, succinimidyl ester, imidazolide or amino functionality. In a particular embodiment, the PSA targets the sequences -Pro-Tyr and Lys-Val-Tyr.

In another embodiment, polymer filament (A) of Figure 4 would have only one attachment site for degradable sequence (B) and a plurality of filaments (A) would be attached to polymer filament (E) with a plurality of complimentary bonding moieties(D). Alternatively, in another embodiment, polymer filament (E) would have only one attachment site for the complimentary bonding moiety (D) and a plurality of filaments (E) would be attached to polymer filament (A) with a plurality of bonding moieties (C). Both of these embodiments will result in graft comb polymers.

The backbone structure for polymer filament (A) and polymer filament (E) of Figure 4 may be the same although they will be functionalized differently with degradable sequences (B), and bonding moieties (C) and (D) components. Furthermore, it will understood by one skilled in the art that additional polymer filaments (not shown) may similarly interact with either polymer filament (A) or (E), thus forming a "multi-decker" polymer system.

Figure 5 illustrates an interpenetrating polymer network containing a water soluble polymer filament (A), which forms hydrophobic micelles(C) through intrapolymer interactions (E). Degradable segments (D) connect polymer filament (A) to interacting moieties (E). A second polymer filament (B), also containing intrapolymer micelles(C), forms an interpenetrating polymer network.

In this mode of the invention two or more polymers are highly viscous when not mixed but form a gel when mixed together, through the formation of an interpenetrating network. By placing a degradable sequence (D) between one of the interacting moieties (E) and the polymer filament (A) a reduction in viscosity results when the degradable sequence (D) interacts with the appropriate component in an ejaculate. By breaking the miscelle interactions (E) of polymer (A) and/or (B) the modulus of the gel is changed.

In a particular embodiment, the degradable sequence (D) of Figure 5 is a peptide capable of cleavage by proteases in an ejaculate.

In a particular embodiment, a hydrolytically labile degradable sequence (D) as shown in Figure 5 is utilized to cause a reduction in the viscosity of the polymer system. In order to accomplish such a viscosity change, one creates a degradable oligo-alpha-hydroxy ester which is terminated with a hydrophobic group (see Figure 6, compound 2). This hydrolytically labile oligo-alpha-hydroxy ester can then be conjugated to a polymerizable moiety and co-polymerized with a water soluble monomer in a ratio of 1 to 50 mole percent. A particular embodiment comprises 7 mole percent of the oligo-alpha-hydroxy ester with the water soluble monomer 2-hydroxypropylmethacrylamide or 2-methacroylethyphosphocholine to form polymer (A) of Figure 5. The resulting polymer (A) can then be mixed with another suitably functionalized polymer filament (B). Polymer filament (B) may be similarly constructed to contain intrapolymer miscelles (C). A mixture of (A) and (B) creates a gel which is stable for days to months at pH ~4 (the normal pH of the vagina).

In a particular embodiment, polymer (B) of Figure 5 is a water soluble zwiterionic polymer containing carboxylic acid groups. When this gel is incubated at pH 7.4 (the pH of semen), the gel network structure can be broken down over several hours by hydrolysis of the oligo-ester crosslinking moieties (D). If the length of the oligo ester is increased, the gel will exhibit reduced viscosity at a more rapid rate because of increased ester hydrolysis. However, in other embodiments, different water soluble monomers can be used for this component such as methacryloyl-phosphocholine based polymers copolymerized with monomers containing carboxylic acid functionalities and other degradable moieties known to those skilled in the art.

Figure 9 illustrates a self-associated degradable polymer system. In this embodiment degradable sequence conjugates (B) are attached to a polymer (A) by well known conjugation techniques. A hydrophobic group (C) is tethered to degradable

sequence (B). Suitable hydrophobic groups include those with a plurality of carbon atoms including but not limited to 4 to 18 carbon atoms depending on the polymer filament (A) and/or the nature of the degradable sequence (B) itself. When this material is subjected to the appropriate component in an ejaculate the degradable sequence will be cleaved into fragments (F) and (G) and the polymer will experience a reduction in viscosity or modulus.

In a particular embodiment, the degradable sequence (B) of Figure 9 is a peptide or sugar capable of cleavage by a protease or enzyme in an ejaculate. In another particular embodiment, a peptide degradable sequence with or without a PEG spacer is conjugated to a water soluble synthetic polymer filament or a water soluble natural polymer filament (A). In a particular embodiment, polymer filament (A) is chitosan. In another particular embodiment, the polymer filament (A) is a poly(acrylic acid)-graft-poly(ethylene oxide) graft comb polymer where the poly(ethylene oxide) graft is terminated in a hydrophobic group and the degradable sequence (B) sits between either the polymer filament (A) or the terminus of the poly(ethylene oxide) and the hydrophobic group (C).

Figure 10 illustrates the conjugation of a moiety (B) to one polymer filament (A) and the conjugation of another moiety (C) to polymer filament (E). Moiety (C) binds moiety (B). When the polymer system comes in contact with the components in an ejaculate (D), one of the components (D) preferentially binds to (C) and displaces (B). The crosslinks are broken resulting in a lower viscosity polymer system or lower modulus polymer gel. In this mode of the invention (A) and (E) may be the same or different polymer filaments.

In a particular embodiment, polymer filament (A) of Figure 10 is selected from the class of water soluble natural and synthetic polymer filaments and to this polymer filament (A) is attached a sugar moiety containing a 1,2 diol (B). In a particular embodiment, polymers (A) and (E) come from but are not limited to the set of approved polymers for human use such poly(acrylic acid) and

poly(hydroxypropylmethacrylamide). Polymer filament (E) is a member of the class of water soluble natural and synthetic polymer filaments as well. To filament (E) are conjugated boronic acid moieties (C). When (A/B) and (E/C) are mixed, a boronic acid ester will form and the material will form a higher molecular weight gel or higher viscosity material. When this material comes in contact with an ejaculate, sugars (D) present within the ejaculate will displace the interaction between (B) and (C) and result in a lower viscosity or lower modulus material.

Figure 11 illustrates the degradation of crosslinking in a polymer system after exposure to an ejaculate. In this embodiment a crosslinking component (B) acts as a crosslinker or gelling agent between two polymer filaments (A) and (E) containing moieties (D) which interact with (B) through covalent, ionic, hydrogen, electrostatic or van der Waals forces to form a higher molecular weight structure. When exposed to an ejaculate, the crosslinking moiety(B) loses contact with the interacting moieties (D) on the polymers (A) and (E). In this mode of the invention (A) and(E) may be the same or different polymer filaments drawing from the classes of water soluble natural and synthetic polymer filaments.

In a particular embodiment of Figure 11, the polymer filaments (A) and (E) are chitosan, the crosslinking component (B) is 2-phospoglycerate and the ejaculate component (F) is granulocyte elastase or enolase which metabolizes 2-phosphoglycerate.

In another particular embodiment of Figure 11, (B) is a crosslinking degradable segment with cationic or anionic groups attached to the ends. Additionally, in another particular embodiment, if (D) is anionic then (B) is cationic or if (D) contains cationic moieties then (B) would be anionic.

Lastly, in another particular embodiment, (B) of Figure 11 is a crosslinking degradable segment containing degradable peptide or sugar sequences as described above with hydrogen bond donors or acceptors attached to the ends. In another particular embodiment, if (D) is a hydrogen bond donor then (B) contains hydrogen bond acceptors

and if (D) contains hydrogen bond acceptors then (B) would contain hydrogen bond donors.

Figure 12 illustrates another mechanism for degradation of crosslinked moieties. In this embodiment a crosslinking substrate(S) acts as a crosslinker or gelling agent between two polymer filaments each containing moiety (D), which interacts with (S) to form a complex (C) and a higher molecular weight structure. The complex remains intact through, ionic, electrostatic, hydrogen or van der Waals. When mixed with a component of an ejaculate (E), the polymer system is degraded because the ejaculate components (E) interact more strongly with (S) than (D) . In this mode of the invention (A) and (F) may be the same or different polymer filaments drawing from the classes of water soluble natural and synthetic polymer filaments.

In a particular embodiment of Figure 12, (A) and (F) are alginate and (S) is a divalent cation like calcium. Additionally, the ejaculate component (E) is a polyvalent ion chelator, like citrate, succinate or phosphate, which is present in an ejaculate.

Sexually Transmitted Diseases

Sexually transmitted diseases that may be prevented by the present invention include, but are not limited to, HIV/AIDS, gonorrhea, Chlamydia,trichomonal infections, human papilloma virus (HPV), syphilis and genital herpes.

Microbicides

Microbicides suitable for use with the present invention include, but are not limited to, entry and/or fusion inhibitors, nonnucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, detergents, surfactants, anti-metabolites and competitive binding inhibitors.

Entry inhibitors prevent HIV from entering a cell while fusion inhibitors prevent interaction between HIV and an outer cell membrane. Examples of each include Enfuvirtide (Fuzeon, T-20), AMD11070, PRO 542, SCH-C, T-1249, TNX-355, cyanovirin and the like.

Nonnucleoside Reverse Transcriptase Inhibitors block reverse transcriptase, preventing HIV replication. Nonnucleoside Reverse Transcriptase Inhibitors include Delavirdine (Rescriptor), Efavirenz (Sustiva), Nevirapine (Viramune), Calanolide A, Capravirine, Epivir, Hivid, TMC125 and the like.

Nucleoside Reverse Transcriptase Inhibitors function to block reverse transcriptase in order to stunt or block HIV replication. Examples of Nucleoside Reverse Transcriptase Inhibitors include Abacavir (Ziagen), Abacavir+Lamivudine+Zidovudine (Trizivir), Didanosine (Videx, ddl), Emtricitabine (Emtriva, FTC), Lamivudine (Epivir, eTC), Lamivudine+Zidovudine (Combivir), Stavudine (Zerit, d4t), Tenofovir DF (Viread), Delavirdine (Rescriptor) Zalcitabine (Hivid, ddc) and Zidovudine (Retrovir, AZT, ZDR).

Protease inhibitors are a broad class of antiviral drugs that block a critical protein necessary for HIV replication. Examples of protease inhibitors include Amprenavir (Agenerase), Atazanavir (Reyataz), Fosamprenavir (Lexiva, 908), Indinavir (Crixivan), Lopinavir+Ritonavir (Kaletra), Nelfinavir (Viracept), Ritonavir (Norvir), Emtriva, Saquinavir (Fortovase, Invirase), Invirase, Agenerase and the like.

Examples of detergents and surfactants include octoxynol-9, chlorhexidine, and benzalkonium chloride and the like. Examples of anti-metabolites of use in the present invention include AZT and the like. Additionally, competitive binding inhibitors, such as dextran, may also be utilized in the present invention.

Microbicides of the present invention that destroy microbes, such as viruses and bacteria, include nonoxynol-9 (N-9), C31G, Carbopol 974P, Carrageenan, Cyanovirin-N, Hydroxyethyl cellulose, PRO 2000, UC-781 and the like.

Microbicides of the present invention that function as birth control agents include, but are not limited to, ethinyl estradiol, norethindrone, levonorgestrel, ethynodiol diacetate, ethynodiol diacetate, RU486, mifepristone, mifegyne, mifeprex and the like.

Microbicides of the present invention that function as hormone replacement agents include, but are not limited to, estrogen, progestin, estrogen and progestin, and the like.

The polymer system of the present invention can be applied to an oral, rectal or vaginal cavity.

In one embodiment of the present invention, the polymer system is composed of two distinct low viscosity polymers. Upon mixing the two polymers, a gel forms due to the formation of interactions between the two polymers. In a particular embodiment, such interaction is a crosslink. These interactions may be temporarily disrupted under mechanical or sheer stresses, which may allow sheer thinning. Additionally, upon exposure to an ejaculate, the interactions may be degraded or destroyed by a component in the ejaculate creating a low viscosity fluid.

Examples

It should be appreciated by those skilled in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute particular modes for its practice. However, those of skill in the art should appreciate, in light of the present disclosure, that many changes can be made in the specific embodiments disclosed herein which will still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Preparation of Ejaculate-Degradable Polymers

Synthesis of ejaculate-degradable polymers as illustrated in Figure 6.

Synthesis of the Butyl oligo-glycolate (1): 1,4,-Dioxane-2,5-dione (5.0g, 43.1 mmol), 1-pentanol (2.2g, 28.7 mmol) and 0.1g tin octanoate were charged in a 20 mL reactor and heated to 120 °C for 24 hours with stirring. The resultant solution was poured into $CHCl_3$ and filtered through a bed of SiO_2 eluting with $CHCl_3$/isopropanol. The resulting mixture of oligomers was collected and dried *in vacuo* (3.4 g).

Synthesis of succinic acid mono-[1-methyl-2-(2-methyl-acryloylamino)-ethyl] ester (2): (1) (2g, 14 mmol) and succinic anhydride (2.10 g, 21 mmol) were dissolved in 10 mL $CHCl_3$. Triethyl amine (2.82 g, 28 mmol) and 4-dimethylaminopropylamine (DMAP) (170 mg, 1.3 mmol) were added along with 3 mL of DMF. The reaction turned purple. The materials were washed with 1M HCl and a concentrated brine solution (3 x 50 mL). The organic layer was filtered through a silica plug eluting first with $CHCl_3$ and then with $CHCl_3$/methanol. The solvent was removed under vacuum yielding a white crystalline solid (2.2 g, 10 mmol, 65%).

Coupling of HPMA and (2) to form the degradable HPMA Monomer terminated in a butyl group (2): Succinic acid mono-[1-methyl-2-(2-methyl-acryloylamino)-ethyl] ester **(2)** (1.2 g, 4.9 mmol) was dissolved in 4 mL $CHCl_3$, which had been dried over 4Å molecular sieves. To this solution was added N,N'-carbonyl diimidazole (CDI) (0.72g,

4.4 mmol). The reaction was accompanied by bubbling and release of CO_2. After stirring for 5 hours under a nitrogen gas atmosphere, 2-hydroxypropyl methacrylate (HPMA) was added (2.65g, ~5 mmol) and the reaction was allowed to stir overnight. The resulting material was extracted three times with pH 5 phosphate buffer to remove any unreacted acid and imidazole. The organic layer was concentrated and the material was filtered through a silica plug eluting with $CHCl_3$ and then methanol. The resulting product was collected and utilized in Experiment 2.

Example 2: Degradation in pH 4 over 4 hours

After the gel had formed, the material was vigorously mixed with pH 7.4 TRIS buffer and its viscosity was measured on an TA-instruments rheometer versus time at a sheer rate 1 s^{-1}. Stress-strain data was collected for 5 minutes and then the sample was allowed to sit undisturbed between time points. The sample showed a significant amount of degradation after 3.5 hours. As is illustrated in Figure 8, viscosity of the gel decreased over time.

Example 3: Rhelogical Properties After Mixing

Figure 7 illustrates the change in rhelogical properties of the individual components of a polymer system, as well as the resulting polymer system.

The compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of particular embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods and/or in the steps or in the sequence of the methods described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain related reagents may be substituted for the reagents described herein while the same or similar results would be achieved. All such substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

Table 1

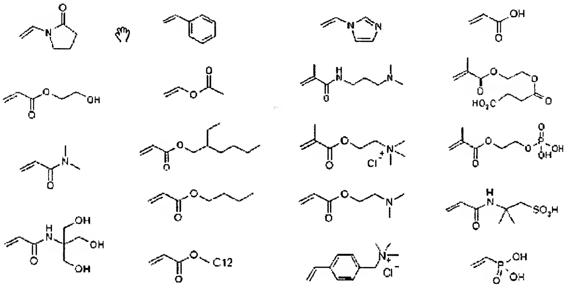
Components of Human Semen in order of concentration (mg/ml)

Protein	Sialic Acid	Cholesterol	Sorbitol
Carbohydrates	Glucose	Glutantione	Lipid P
Phospholipids	Lactoferrin	Ca	Uric Acid
Albumin	K	Carnitine	Tranferrin
Citrate	Spermine	Creatine	Creatinine
Na	Phosphate	Pyruvic Acid	Ammonia
Fructose	Triglycerides	Zn	
Choline	Lactic Acid	Ascorbic Acid	
Cl	Inositol	Mg	
Glycerol Phosphocholine	Urea	Glutamic acid	

Table 2 Active enzymes in semen.

Protein	Substrate	Reference
Alanyl aminopeptidase(AAPS)		
alanyl aminopeptidase(ApN)		
granulocyte elastase enolase	2-phosphoglycerate	
angiotensin converting enzyme(ACE)	Phenylalanyl-glycyl-glycine	
dipeptidylpeptidase IV		
kallikrein hK2 (Kininogenase)	Arg-Glu-Glu Arg-Arg	
Gastricsin		
matrix metalloproteinases (MMP-2 and MMP-9)	ECM Components	
Kallikrein hK3	SSIYSQTEEQ or Arg-Pro-Tyr or lys-val-tyr or IYS	

Table 3. examples of acylic monomers which may be used in polymer systems described herein.



We Claim:

1. A composition comprising; a polymer system containing degradable sequences susceptible to degradation upon exposure to an ejaculate.

2. The composition of claim 1, wherein said degradable sequences are susceptible to degradation by an acid, base, protein and semen.

3. The composition of claim 1, further comprising a microbicide.

4. The composition of claim 3, wherein said microbicide is associated with said polymer system.

5. The composition of claim 3, wherein said microbicide is conjugated to said polymer system.

6. The composition of claim 3, wherein said microbicide is selected from the group consisting of fusion inhibitors, nonnucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, spermicides, entry inhibitors, spermicides, agents that prevent fertility, agents that promote fertility and hormone replacement agents.

7. The composition of claim 3, wherein said microbicide is released from the polymer system upon exposure to an ejaculate.

8. The composition of claim 1, wherein said polymer system includes a polymer selected from the group consisting of polyethylene glycol, polypropropylene glycol, polyhydroxypropyl methacrylamide, poly-amino acids, poly-acrylates, poly-alpha-hydroxy acids and poly-caprolactone.

9. The composition of claim 1, wherein said degradation includes chemical and enzymatic degradation.

10. The composition of claim 9, wherein said chemical degradation is selected from the group consisting of hydrolytic cleavage and proteolytic cleavage.

11. The composition of claim 10, wherein said chemical degradation is due to an agent selected from the group consisting of prostate specific antigen, peptidases, hyaluronidases, alpha glucosidase, beta glucosidase, lysophospholipases, lysozyme, mannosidases, pepsinogen I, pepsinogen II, pepsinogen III and phospholipase. .

12. The composition of claim 1, wherein said degradation results in decreased viscosity of said composition.

13. The composition of claim 1, wherein said degradable sequence is selected from the group consisting of oligomers of the alpha-hydroxyesters; peptide sequences including ARG-Pro-Tyr; peptide sequences including Lys-Val-Tyr; peptide sequences similar to semenogellin; peptide sequences including SSIYSQTEEQ; shorter homologs of SSIYSQTEEQ; shorter homologs of SSIYSQTEEQ including serine and tyrosine; peptides containing a positively charged amino acid in the first position a neutral amino acid in the second position and tyrosine in the third position; peptides containing a positively charged amino acid in the first position a neutral amino acid in the second position and tyrosine in the third position with additional amino acids on both the C and N terminus, hyaluronic acid based polymers; sub-units of hyaluronic acid and a degradable sequence conjugate.

14. A method comprising; administering to an individual a polymer system containing degradable sequences susceptible to degradation upon exposure to an ejaculate.

15. The method of claim 14, wherein said degradable sequences are susceptible to degradation by an acid, base, protein and semen.

16. The method of claim 14, further comprising a microbicide.

17. The method of claim 16, wherein said microbicide is associated with said polymer system.

18. The method of claim 16, wherein said microbicide is conjugated to said polymer system.

19. The method of claim 16, wherein said microbicide is selected from the group consisting of fusion inhibitors, nonnucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, spermicides, entry inhibitors, spermicides, agents that prevent fertility, agents that promote fertility and hormone replacement agents.

20. The method of claim 16, wherein said microbicide is released from the polymer system upon exposure to an ejaculate.

21. The method of claim 14, wherein said polymer system includes a polymer selected from the group consisting of polyethylene glycol, polypropropylene glycol, polyhydroxypropyl methacrylamide, poly-amino acids, poly-acrylates, poly-alpha-hydroxy acids and poly-caprolactone.

22. The method of claim 14, wherein said degradation includes chemical and enzymatic degradation.

23. The method of claim 22, wherein said chemical degradation is selected from the group consisting of hydrolytic cleavage and proteolytic cleavage.

24. The method of claim 22, wherein said chemical degradation is due to prostate specific antigen, alpha glucosidase, beta glucosidase, lysophospholipases, lysozyme, mannosidases, pepsinogen I, pepsinogen II, pepsinogen III and phospholipase. .

25. The method of 14, wherein said degradation results in decreased viscosity of said composition.

26. The method of claim 14, wherein said composition is capable of sheer thinning when exposed to mechanical force.

27. The method of claim 14, wherein said administration is for a purpose selected from the group consisting of prevention of a sexually transmitted disease, prevention of fertility, promotion of fertility and hormone replacement therapy.

28. The method of claim 27, wherein said sexually transmitted disease is selected from the group consisting of HIV, gonorrhea, Chlamydia, human papiloma virus, herpes and syphilis.

29. The method of claim 14, wherein said administration is anal, vaginal or oral.

30. The method of claim 14, wherein said degradable sequence is selected from the group consisting of oligomers of the alpha-hydroxyesters; peptide sequences including ARG-Pro-Tyr; peptide sequences including Lys-Val-Tyr; peptide sequences similar to semenogellin; peptide sequences including SSIYSQTEEQ; shorter homologs of SSIYSQTEEQ; shorter homologs of SSIYSQTEEQ including serine and tyrosine; peptides containing a positively charged amino acid in the first position a neutral amino acid in the second position and tyrosine in the third position; peptides containing a positively charged amino acid in the first position a neutral amino acid in the second position and tyrosine in the third position with additional amino acids on both the C and N terminus, hyaluronic acid based polymers; sub-units of hyaluronic acid and a degradable sequence conjugate.

31. A method of delivering a microbicide comprising; administering to an individual a polymer system containing degradable sequences susceptible to degradation upon exposure to an ejaculate.

Abstract

The polymer systems of the present invention include degradable sequences hat degrade upon contact with an ejaculate. They may further provide microbicides associated with or conjugated to the polymer systems. The polymer systems of the present invention are of use for the prevention of sexually transmitted disease, the prevention of fertility, the promotion of fertility and/or for hormone replacement therapy.

Figure 1

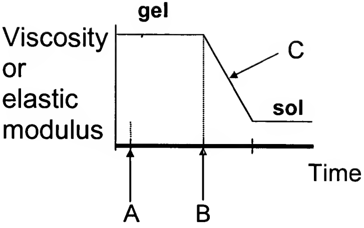


Figure 2

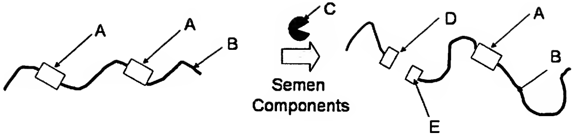


Figure 3

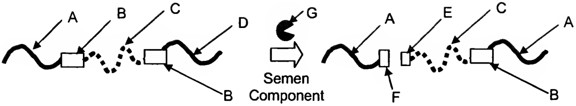


Figure 4

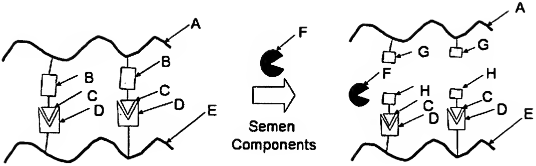


Figure 5

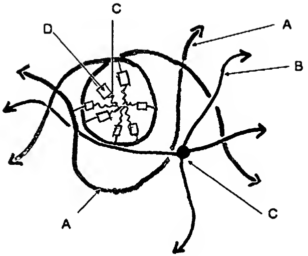
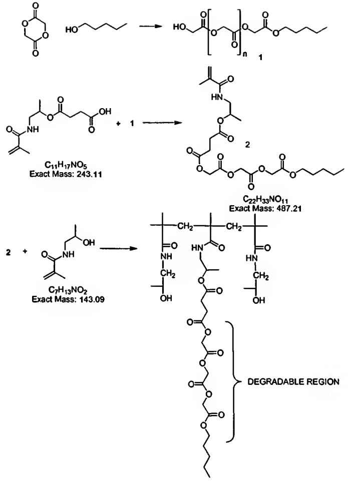
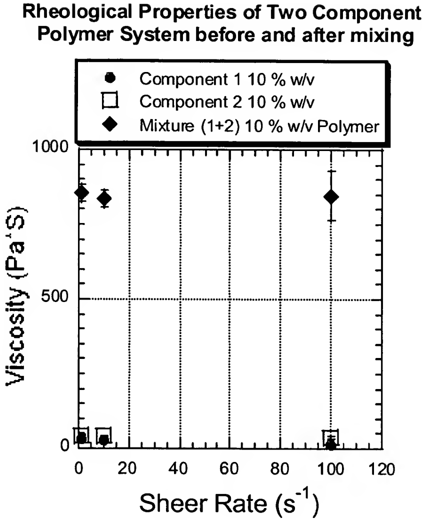


Figure 6



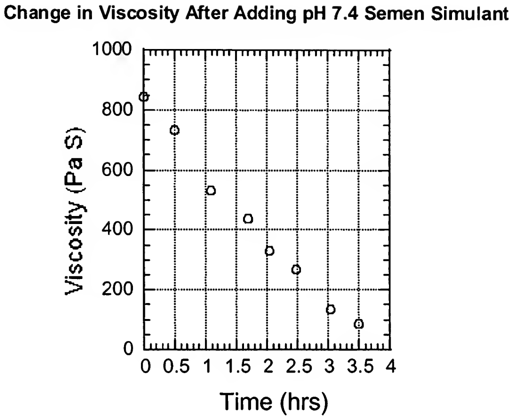
HO
HO
n
1
OH
NH
+ 1
HN
2
$C_{11}H_{17}NO_5$
Exact Mass: 243.11
$C_{22}H_{33}NO_{11}$
Exact Mass: 487.21
2 +
OH
NH
$C_7H_{13}NO_2$
Exact Mass: 143.09
CH_2
CH_2
NH
HN
HN
OH
OH
DEGRADABLE REGION

Figure 7



Rheological Properties of Two Component
Polymer System before and after mixing
Component 1 10 % w/v
Component 2 10 % w/v
Mixture (1+2) 10 % w/v Polymer
1000
500
0
Viscosity (Pa·S)
0
20
40
60
80
100
120
Sheer Rate (s-1)

Figure 8



Change in Viscosity After Adding pH 7.4 Semen Simulant
1000
800
600
400
200
0
Viscosity (Pa S)
0 0.5 1 1.5 2 2.5 3 3.5 4
Time (hrs)

Figure 9

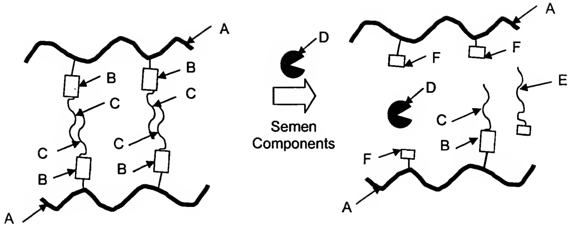


Figure 10

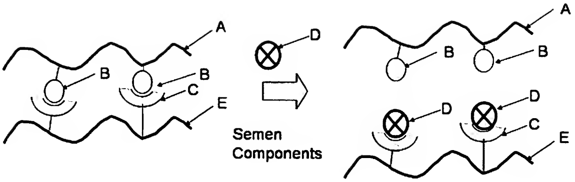


Figure 11

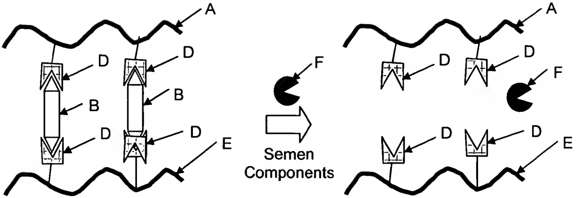


Figure 12

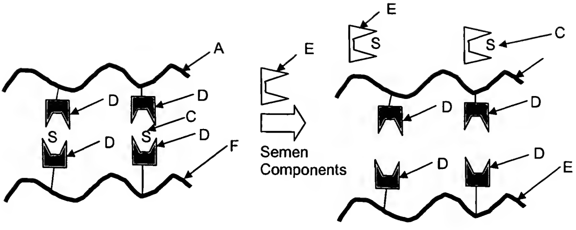


Figure 13